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TITLE: Molecular Targeting of the P13K/Akt Pathway to Prevent the Development Hormone Resistant Prostate Cancer

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Recently the PI3K/Akt pathway has been found to be a significant factor in the development and progression of prostate cancer. It is our belief that the PI3K/Akt pathway is the critical pathway that is maintaining survival by blocking apoptosis in the absence of hormonal stimulation. We will use molecular targeting to inhibit the phosphorylation of Akt. Celecoxib is a FDA approved COX-2 inhibitor, however unique to celecoxib is its ability to inhibit the phosphorylation of Akt. This effectively turns off the PI3k/Akt pathway leading to apoptosis. Celecoxib has been shown to induce apoptosis in a number of different malignancies. Unfortunately the IC50 of celecoxib is less than usually clinically obtainable. Therefore, in an attempt to improve upon the Akt activity and decrease the IC50 concentration to clinically obtainable levels, Chin et al. synthesized multiple 2nd and 3rd generation compounds. These newer compounds have significantly lower IC50 and thus therapeutic levels can be obtained clinically. We will use celecoxib and these newer compounds to evaluate the effects of combined PI3K/Akt inhibition and androgen ablation.

15. SUBJECT TERMS
No subject terms provided.

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Introduction

Our principle hypothesis for the proposal is that combined inhibition of the PI3K/Akt pathway and the androgen pathway will result in a synergistic effect to include: increased apoptosis, decreased proliferation, and a decreased tumor growth.

The rational for our proposal is that hormone refractory prostate cancer has over expression of the PI3K/Akt pathway both at the genomic and protein level implying a significant role in prostate cancer proliferation. Akt has multiple downstream effectors all of which promote growth and survival. There is a direct connection between Akt and the AR that allows Akt to directly activate the AR, and thus activating the androgen pathway. We believe selectively inhibiting both the PI3K/Akt and androgen pathway will cause a synergistic effect. Thus, with combined inhibition, apoptosis will be increased with a corresponding decrease in proliferation ultimately leading to the purpose of our study; a prolongation in patient's survival with metastatic prostate cancer.

Body

Specific Aim 1: Assess the Effectiveness of Combined Hormonal Ablation and PI3K/Akt Pathway Inhibition *In vitro* using a Human Prostate Tissue-Based Organ Culture Model System.

Task 1: Determine the Utility of Using Precision Cut Thin Tissue Sections from Non Radical Prostatectomy Specimens

Currently, we have made no progress in the last 3 years. The conditions here have not been at all conducive to further this project. Difficulties faced over the last 3 years include a persistent lack of support from the Department of Surgery and the College of Medicine. This lack of support was secondary but not limited to a lack of a sitting Department Head or a Dean committed to research or a Section Head, during a majority of this project. Also during this period the section of urology had lost a number of faculty include the head of the section with further responsibility being placed on myself to keep the section and residency program viable. Given these series of events this project has been lingering for the last three years per our multiple discussions. At this time an administrative decision above my level was made to close this project. I had been in discussions with the local VA facility to move the project there however this decision was made prior to my obtaining approval form the parties involved.

Task 2: Determine the Optimal Timing for Evaluation the Effects of a Combined Inhibition.

See above

Task 3: Assessing the Effectiveness of Combined Hormonal Ablation and

PI3K/Akt Pathway Inhibition *In vitro* using a Thin Tissues Sections

See above.

Specific Aim 2 and 3:

Have not begun at this time see above.

Key Research Accomplishments:

None in the last year.

Reportable Outcomes

We have no reportable outcomes at this time.

Conclusions

The primary hurdle we had to face is the local academic/financial environment; unfortunately these problems have been identified but never address thus we could restart this project.

References – None at this time.

Appendices – None at this time.